VOLUME 32 · NUMBER 18 · JUNE 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ONCOLOGY GRAND ROUNDS

Second-Line Therapy in Non–Small-Cell Lung Cancer: The DELTA Between Different Genotypes Widens

Alona Zer and Natasha B. Leighl, *Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada*

See accompanying article on page 1902

The Oncology Grand Rounds series is designed to place original reports published in the Journal *into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in* Journal of Clinical Oncology, *to patients seen in their own clinical practice.*

A 55-year-old woman with a prior 15-pack-year smoking history presented with persistent cough and minor weight loss. Chest imaging revealed two masses in the right upper lobe, mediastinal adenopathy, a right-sided pleural effusion, and pleural nodules. Video-assisted pleuroscopy identified lung adenocarcinoma in the pleura and malignant effusion, with cells that were positive for CK7 and thyroid transcription factor 1(TTF-1) and negative for CK20, p63, and calretinin. Testing for epidermal growth factor receptor (*EGFR*) mutation and *ALK* rearrangement was initiated, but the patient wanted to start treatment immediately rather than wait for test results, which typically requires 2 to 4 weeks. She was enrolled onto a clinical trial and was randomly assigned to receive standard pemetrexed-cisplatin. She experienced a partial response, but she had substantial symptoms, including nausea refractory to antiemetics and significant fatigue. She requested a break from chemotherapy after six cycles and developed symptomatic progression in the lung and pleura within 10 weeks. Meanwhile, molecular testing showed neither *EGFR* mutation in exons 19 or 21 nor *ALK* rearrangement in her tumor. The patient was reluctant to start second-line chemotherapy because of concerns about toxicity. She received palliative radiotherapy to the lung and growing pleural mass with some pain relief, and the palliative care team was consulted for additional support in symptom control. At this juncture, the adverse effects from chemotherapy have resolved, and she has an Eastern Cooperative Oncology Group performance status of 1. Second-line docetaxel is recommended, but she inquires about nonchemotherapy options.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

Key goals of systemic therapy in advanced non–small-cell lung cancer (NSCLC) are the improvement of symptoms, quality of life, and survival with minimal toxicity. Second-line therapy in advanced NSCLC was established in 2000 with the publication of two randomized trials of second-line docetaxel that demonstrated improved survival, symptom control, and quality of life compared with best supportive care and with vinorelbine or ifosfamide chemotherapy.[1-3] By 2009, the American Society of Clinical Oncology Clinical Practice Guideline for systemic therapy in stage IV lung cancer recognized four potential options for second-line therapy: docetaxel, pemetrexed, erlotinib, and gefitinib.[4] Pemetrexed is associated with superior survival in nonsquamous carcinoma, and docetaxel appears superior in squamous carcinoma.[5,6] Among molecularly unselected patients with pretreated advanced NSCLC, erlotinib is superior to placebo with respect to survival and quality of life.[7,8] Although gefitinib is not superior to placebo with respect to survival and quality of life, it has demonstrated noninferior outcomes when compared with second-line docetaxel in advanced NSCLC,[9] and has been accepted as a standard second-line treatment option in molecularly unselected patients, particularly in Asia. Vinflunine and topotecan have activity similar to that of docetaxel as second-line therapy but they have either greater toxicity or worse quality of life.[10,11] A meta-analysis of six randomized trials showed that doublet chemotherapy does not improve survival compared with single-agent therapy but does increase toxicity.[12] Despite multiple options available in the second-line setting, clinical outcomes remain poor. Response rates are, on average, less than 10%, and median survival is 7 to 9 months from the start of second-line therapy.

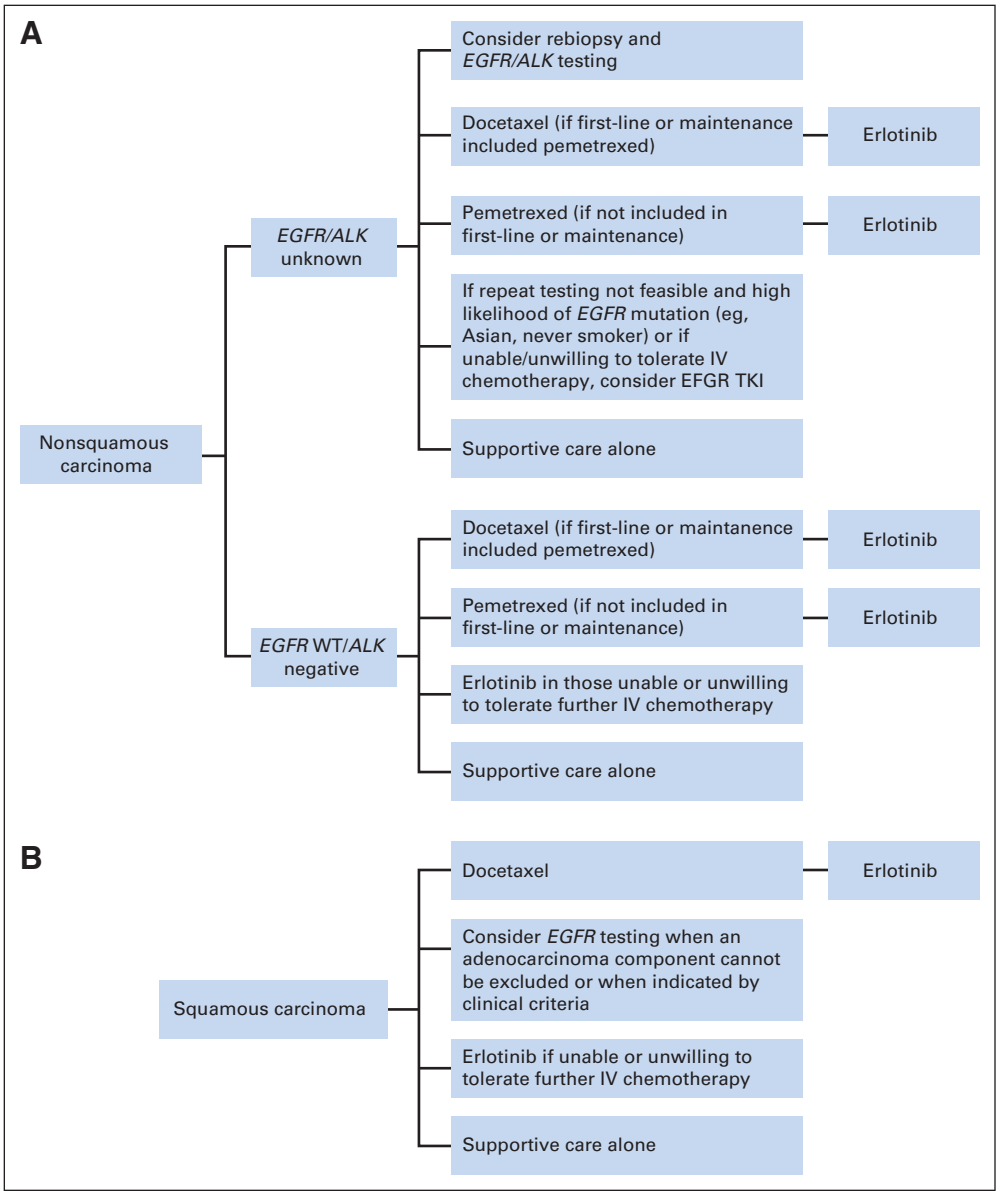

Fig 1. Second-line and subsequent standard treatment options in epidermal growth factor receptor (*EGFR*) –wild-type (WT)/*ALK*-negative, or *EGFR*/*ALK*-unknown advanced non–small-cell lung cancer. IV, intravenous.

Over the past decade, the selection of second-line therapy has become increasingly complex, largely as a result of advances in first-line treatment options and maintenance chemotherapy, as well as targeted therapy options in *EGFR*-mutant and *ALK*-rearranged NSCLC.[13] Among patients with nonsquamous carcinoma, pemetrexed-platinum and bevacizumab-based platinum combinations are widely used for first-line therapy. Maintenance pemetrexed in this population has demonstrated significant gains in survival.[14,15] In patients with squamous carcinoma, pemetrexed use is not recommended. Erlotinib maintenance in unselected patients with NSCLC has also shown a modest survival benefit after completion of platinum doublet therapy.[16] Collectively, these findings make docetaxel or erlotinib the standard second-line treatment options for nonsquamous or squamous lung cancer (Fig 1).

So how do we choose between docetaxel and erlotinib with our current understanding of tumor genotype? What do we do for those patients with insufficient tissue for genotyping? And what can we offer our patients who are unable to or unwilling to tolerate one agent or the other?

SUMMARY OF THE RELEVANT LITERATURE

Treating patients with *EGFR* wild-type advanced NSCLC with an EGFR tyrosine kinase inhibitor (TKI) as first-line therapy yields significantly inferior progression-free and overall survival compared with chemotherapy.[17,18] But what about second-line therapy?

At least nine randomized trials (Table 1),[9,19-26] and four meta-analyses comparing EGFR TKI therapy with second- or third-line chemotherapy have been published,[27-30] with subgroup analyses of outcome by *EGFR* mutation status in five trials and one trial conducted exclusively in patients with *EGFR* wild-type disease.[23] Overall,

Table 1. Phase III Trials of Chemotherapy Versus EGFR TKIs in Previously Treated Patients With Advanced NSCLC

Trial	Reference	Population	*EGFR* Status	Treatment Arms	% of Patients Receiving Second-Line Therapy	No. of Patients	Median PFS (months)	HR	*P*	Median OS (months)	HR	*P*
DELTA	Kawaguchi et al[13]	Asian	Unselected (entire cohort)	Erlotinib 150 mg per day	81	150	Erlotinib 2.0 *v* docetaxel 3.2	1.22	.09	Erlotinib 14.8 *v* docetaxel 12.2	0.91	.53
				Docetaxel 60 mg/m^2 every 21 days	86	151						
			Wild type	Erlotinib 150 mg per day		109	Erlotinib 1.3 *v* docetaxel 2.9	1.57	< .01	Erlotinib 9.0 *v* docetaxel 10.1	1.13	.91
				Docetaxel 60 mg/m^2 every 21 days		90						
			Mutant	Erlotinib 150 mg per day		21	Erlotinib 9.3 *v* docetaxel 7.0	0.82	.91	Erlotinib N/R *v* docetaxel 27.8	0.43	.13
				Docetaxel 60 mg/m^2 every 21 days		30						
PROSE	Lazzari et al[26]	European. Stratified according to VeriStrat good *v* VeriStrat poor	Unselected	Erlotinib 150 mg per day	100	134	N/R			Erlotinib 7.7 *v* docetaxel 9.0	1.14	.31
				Chemotherapy (docetaxel or pemetrexed)		129						
TAILOR	Garassino et al[23]	European	Wild type	Erlotinib 150 mg per day	100	109	Erlotinib 2.4 *v* docetaxel 2.9	0.71	.01	Erlotinib 5.4 *v* docetaxel 8.2	0.73	.05
				Docetaxel 75 mg/m^2 every 21 days or 35 mg/m^2 days 1, 8, and 15 every 28 days		110						
Hellenic Oncology Research Group	Karampeazis et al[25]	European	Unselected	Erlotinib 150 mg per day	53	166	Erlotinib 3.6 *v* docetaxel 2.9		.136	Erlotinib 8.2 *v* docetaxel 10.1	1.0	.99
				Pemetrexed 500 mg/m^2 every 21 days	60	166						
			Wild type	Erlotinib 150 mg per day		55	Favors erlotinib	0.92	N/S	Favors pemetrexed	1.19	N/S
				Pemetrexed 500 mg/m^2 every 21 days		57						
			Mutant	Erlotinib 150 mg per day		6		1.03	N/S		0.52	N/S
				Pemetrexed 500 mg/m^2 every 21 days		5						

(continued on following page)

Table 1. Phase III Trials of Chemotherapy Versus EGFR TKIs in Previously Treated Patients With Advanced NSCLC (continued)

Trial	Reference	Population	*EGFR* Status	Treatment Arms	% of Patients Receiving Second-Line Therapy	No. of Patients	Median PFS (months)	HR	*P*	Median OS (months)	HR	*P*
TITAN	Ciuleanu et al[24]	85% white; chemorefractory	Unselected (entire cohort)	Erlotinib 150 mg per day	100	203	Erlotinib 1.5 *v* chemotherapy 2.0	1.19	.08	Erlotinib 5.3 *v* chemotherapy 5.5	0.96	.73
				Chemotherapy (docetaxel or pemetrexed)		221						
			Wild type	Erlotinib 150 mg per day		75	Favors chemotherapy	1.25	N/S	Favors erlotinib	0.85	N/S
				Chemotherapy (docetaxel or pemetrexed)		74						
			Mutant	Erlotinib 150 mg per day		7		0.71	N/S		1.19	N/S
				Chemotherapy (docetaxel or pemetrexed)		4						
KCSG-LU08-01	Sun et al[21]	Asian, adenocarcinoma, never-smokers	Unselected (entire cohort)	Gefitinib 250 mg per day	100	68	Gefitinib 9.0 *v* pemetrexed 3.0	0.54	< .001	Gefitinib 22 *v* pemetrexed 19	0.8	.37
				Pemetrexed 500 mg/m^2 every 21 days		67						
			Wild type	Gefitinib 250 mg per day		18	Gefitinib 5.9 *v* pemetrexed 2.7	0.56	.099	N/R		
				Pemetrexed 500 mg/m^2 every 21 days		20						
			Mutant	Gefitinib 250 mg per day		16	Gefitinib 15.7 *v* pemetrexed 2.9	0.3	.005	N/R		
				Pemetrexed 500 mg/m^2 every 21 days		17						
ISTANA	Lee et al[22]	Asian	Unselected	Gefitinib 250 mg per day	100	82	Gefitinib 3.3 *v* docetaxel 3.4	0.73	.04*	Gefitinib 14.1 *v* docetaxel 12.2	0.87	.4
				Docetaxel 75 mg/m^2 every 21 days		79						

(continued on following page)

Table 1. Phase III Trials of Chemotherapy Versus EGFR TKIs in Previously Treated Patients With Advanced NSCLC (continued)

Trial	Reference	Population	*EGFR* Status	Treatment Arms	% of Patients Receiving Second-Line Therapy	No. of Patients	Median PFS (months)	HR	*P*	Median OS (months)	HR	*P*
INTEREST	Douillard et al[20]	75% white	Unselected (entire cohort)	Gefitinib 250 mg per day	Approximately 85	733	Gefitinib 2.2 *v* docetaxel 2.7	1.04	.47	Gefitinib 7.6 *v* docetaxel 8.0	1.02	N/S
				Docetaxel 75 mg/m^2 every 21 days		733						
			Wild type	Gefitinib 250 mg per day		125	Favors docetaxel	1.24	.14	Gefitinib 6.4 *v* docetaxel 6.0	1.02	.91
				Docetaxel 75 mg/m^2 every 21 days		142						
			Mutant	Gefitinib 250 mg per day		15	Favors gefitinib	0.16	.001	Gefitinib 14.2 *v* docetaxel 16.6	.83	.60
				Docetaxel 75 mg/m^2 every 21 days		16						
V-15-32	Maruyama et al[19]	Asian	Unselected	Gefitinib 250 mg per day	Approximately 85	245	Gefitinib 2.0 *v* docetaxel 2.0	0.9	.34	Gefitinib 11.5 *v* docetaxel 14.0	1.12	.33
				Docetaxel 60 mg/m^2 every 21 days		244						

Abbreviations: DELTA, Docetaxel and Erlotinib Lung Cancer Trial; EGFR, epidermal growth factor receptor; HR, hazard ratio (reported with 95% CI [not shown]); INTEREST, IRESSA NSCLC Trial Evaluating Response and Survival Against Taxotere; ISTANA, IRESSA As Second-Line Therapy in Advanced NSCLC- Korea; KCSG-LU, Korean Cancer Study Group-Lung; N/R, not reported; N/S, not significant; NSCLC, non–small-cell lung cancer; OS, overall survival; PFS, progression-free survival; PROSE, Randomized Proteomic Stratified Phase III Study of Second Line Erlotinib Versus Chemotherapy in Patients With Inoperable Non–Small-Cell Lung Cancer; TAILOR, Tarceva Italian Lung Optimization Trial; TITAN, Tarceva In Treatment of Advanced NSCLC; TKI, tyrosine kinase inhibitor.
*90% CI [not shown].

trials in molecularly unselected patients show similar survival outcomes for those treated with EGFR TKIs or chemotherapy. In Asian studies of molecularly unselected patients, second-line treatment with EGFR TKIs is consistently comparable to chemotherapy, with two trials demonstrating better progression-free survival (PFS) with the TKI,[21,22] likely because of the higher frequency of *EGFR*-mutant NSCLC in that population. In patients whose tumors are positive for *EGFR* mutations, most trials and meta-analyses demonstrate better PFS but not overall survival (OS) with second-line EGFR TKI therapy compared with chemotherapy, likely because of crossover and the efficacy of EGFR TKI therapy in the third-line setting.

But in patients with *EGFR* wild-type NSCLC, outcomes have not been consistent across trials. In the INTEREST (IRESSA NSCLC Trial Evaluating Response and Survival Against Taxotere) trial, 267 patients with *EGFR* wild-type NSCLC were identified retrospectively, and no significant differences were found in PFS or OS between second-line gefitinib and docetaxel.[20] TAILOR (Tarceva Italian Lung Optimization Trial) prospectively examined the outcomes of 219 patients with *EGFR* wild-type NSCLC randomly assigned to either docetaxel or erlotinib[23] and reported that docetaxel was superior to erlotinib for both PFS and OS, with a median survival difference of nearly 3 months favoring chemotherapy (8.2 *v* 5.4 months; adjusted hazard ratio [HR], 0.73; 95% CI, 0.53 to 1.00; $P = .05$). TAILOR is the first study to demonstrate improved survival with docetaxel over erlotinib in patients with *EGFR* wild-type NSCLC.

In the accompanying article, the DELTA (Docetaxel and Erlotinib Lung Cancer) trial investigators report findings in molecularly unselected patients treated with either docetaxel or erlotinib after first-line chemotherapy.[31] In the preplanned subgroup analysis by *EGFR* genotype, docetaxel yielded superior PFS of 3.2 months compared with 2.0 months for erlotinib in patients with *EGFR* wild-type NSCLC (HR, 1.22 for erlotinib compared with docetaxel; 95% CI, 1.09 to 1.94; $P = .01$), although no significant difference in OS was observed. The findings in DELTA support the results of the TAILOR trial and are similar to a recent meta-analysis that demonstrated improved PFS with second-line chemotherapy compared with EGFR TKIs in the subgroup of patients with *EGFR* wild-type NSCLC (HR, 1.23; 95% CI, 1.05 to 1.46).[27] All of these studies used different genotyping methods and the sensitivity of mutation detection varied; however, the studies were able to ascertain genotype in a proportion of patients ranging from 20% in the INTEREST trial to 100% in the TAILOR trial.[20,23] Surprisingly, responses to EGFR TKIs in patients with *EGFR* wild-type NSCLC were seen in both TAILOR (3%) and DELTA (5.6%), highlighting the fact that molecular testing in lung cancer, as with testing for all other diseases, is subject to potential bias from false-negative and perhaps even false-positive results. Acknowledging these limitations, there is a growing body of evidence that EGFR TKIs and chemotherapy are not equal in terms of outcome when *EGFR* status is taken into account. In particular, the balance of evidence favors second-line chemotherapy for patients with *EGFR* wild-type NSCLC able to withstand its toxicities, with at least one trial (TAILOR) demonstrating better survival, and others including DELTA showing better PFS. Similarly, the evidence favors use of EGFR TKIs for patients with mutant *EGFR* NSCLC who are still TKI naive, recognizing that multiple trials have reported greater PFS but none has yet reported better OS.

It is important to recall that the comparator for these second-line EGFR TKI trials is chemotherapy, not placebo. The National Cancer Institute of Canada Clinical Trials Group BR.21 trial (Randomized Placebo Controlled Study of Erlotinib [OSI Study OSI–774, Tarceva] versus Placebo in Patients with Incurable Non–Small-Cell Lung Cancer Who Have Failed Standard Therapy for Advanced or Metastatic Disease) suggests that the benefit of erlotinib compared with placebo is not restricted to *EGFR* mutation–positive patients. In the subgroup of patients with known *EGFR* status, the HR for survival in the *EGFR* wild-type subgroup was 0.74 ($P = .09$) for erlotinib versus placebo and 0.55 ($P = .12$) in *EGFR*-mutant NSCLC.[32] The SATURN (Sequential Tarceva in Unresectable NSCLC) trial further supports a survival benefit with erlotinib as maintenance therapy compared with placebo in a subgroup analysis of patients with *EGFR* wild-type NSCLC.[33]

SUGGESTED APPROACHES TO MANAGEMENT

TAILOR, DELTA, and other recent trials emphasize that we cannot afford to ignore *EGFR* status in our selection of second-line therapy.

In our opinion, for patients with known *EGFR* wild-type NSCLC, docetaxel (for those previously treated with pemetrexed or with squamous carcinoma) is the best option currently available for second-line therapy. Although not directly tested in this trial, pemetrexed would be our preferred option for patients with nonsquamous carcinoma who have not received prior pemetrexed as part of first-line or maintenance therapy. For those whose tumors harbor *EGFR* mutations, treatment with EGFR TKIs as soon as possible is ideal, preferably in the first-line setting, with demonstration of greater PFS and quality of life, although not OS. For those with *EGFR*-mutant NSCLC who have progressed on EGFR TKI therapy, the current second-line standard remains chemotherapy (most commonly platinum-doublet therapy), although there is an opportunity for these patients to participate in ongoing trials of EGFR inhibition with chemotherapy, newer irreversible inhibitors of EGFR, or with other combinations.

Despite advances in technology, not all patients with advanced NSCLC have sufficient tissue for molecular testing. It is estimated that between 15% and 35% of patients may not have sufficient samples for genotyping.[32,34] Some patients may be amenable to repeat tumor sampling, but others may be unable to tolerate a repeat biopsy. Although methods for collection and testing of plasma or circulating DNA for mutation testing are evolving, these are not yet standardized nor are they available for all patients as part of routine practice.

So what should we do for those patients whose nonsquamous NSCLC has unknown *EGFR* status? When possible, these patients should be considered for an attempt at repeat testing. When this is not feasible, an open conversation about the pros and cons of chemotherapy versus EGFR TKIs should be discussed with patients. Although EGFR TKI therapy may be less toxic than docetaxel, most of our patients will have *EGFR* wild-type NSCLC and thus will be less likely to benefit from EGFR TKI therapy. A preferred strategy would be to offer second-line chemotherapy when *EGFR* status is unknown. For those who are unable to or unwilling to tolerate second-line therapy, it would be reasonable to discuss the option of erlotinib, assuming they are not candidates for further chemotherapy. If there is a high clinical suspicion of an *EGFR* mutation and EGFR TKI is recommended as second-line therapy, patients should be informed of the risks of deteriorating without a chance of chemotherapy if they have wild-type disease (although studies have shown no difference in OS in the

second-line setting). In the ideal situation, patients would have the option of all three lines of therapy, first- and second-line chemotherapy with erlotinib after chemotherapy failure, as well as access to clinical trials and further molecular profiling for other oncogenic drivers for those with *EGFR* wild-type, *ALK*-negative NSCLC to help further identify potential options for active therapy.

Another important option for patients and oncologists to discuss is the option of supportive care alone after failure of first-line and/or maintenance therapy. It is estimated that only 30% to 50% of our patients receive second-line therapy, with the rest pursuing supportive care alone.[35,36] Factors associated with second-line chemotherapy treatment include good performance status, female sex, nonsquamous histology, younger age and, in one US analysis, insurance type and longer duration of first-line therapy.[35-37] Despite progress in lung cancer treatment, response rates remain less than 10%, and even in highly selected patients, median survival is 7 to 9 months from the start of second-line treatment. Thus, choosing supportive care alone after first-line chemotherapy failure remains an important option for patients with advanced NSCLC, particularly in light of modest benefits, potentially significant treatment toxicity, and costs.

Our patient declined additional chemotherapy. Instead, she enrolled onto a clinical trial of second-line erlotinib plus a novel agent and was randomly assigned to the erlotinib control arm in which she had tumor progression within 4 months, with worsening chest pain and a decline in performance status. At this point she agreed to proceed with docetaxel. Within 3 weeks, she noticed a reduction in pain and dyspnea. She has had one admission for febrile neutropenia, requiring subsequent docetaxel dose reduction, but she has received six cycles with partial response, improved performance status, and reduced pain such that she has been able to stop all opioid pain medication. She continues on treatment and is also participating in a molecular profiling study to better understand potential oncogenic drivers and next steps in treatment for her *EGFR* wild-type nonsquamous NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** Natasha B. Leighl, Roche Canada (Clinical Trial funding to University Health Network) **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000

2. Fossella FV, DeVore R, Kerr RN, et al: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non–small-cell lung cancer previously treated with platinum-containing chemotherapy regimens: The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 18:2354-2362, 2000

3. Dancey J, Shepherd FA, Gralla RJ, et al. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy: Results of a prospective, randomized phase III trial. Lung Cancer 43:183-194, 2004

4. Azzoli CG, Baker S Jr, Temin S, et al: American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non–small-cell lung cancer. J Clin Oncol 27:6251-6266, 2009

5. Hanna N, Shepherd FA, Fossella FV, et al: Randomized phase III trial of pemetrexed versus docetaxel in patients with non–small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589-1597, 2004

6. Scagliotti G, Hanna N, Fossella F, et al: The differential efficacy of pemetrexed according to NSCLC histology: A review of two Phase III studies. Oncologist 14:253-263, 2009

7. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005

8. Thatcher N, Chang A, Parikh P, et al: Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 366:1527-1537, 2005

9. Kim ES, Hirsh V, Mok T, et al: Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): A randomised phase III trial. Lancet 372:1809-1818, 2008

10. Ramlau R, Gervais R, Krzakowski M, et al: Phase III study comparing oral topotecan to intravenous docetaxel in patients with pretreated advanced non–small-cell lung cancer. J Clin Oncol 24:2800-2807, 2006

11. Krzakowski M, Ramlau R, Jassem J, et al: Phase III trial comparing vinflunine with docetaxel in second-line advanced non–small-cell lung cancer previously treated with platinum-containing chemotherapy. J Clin Oncol 28:2167-2173, 2010

12. Di Maio M, Chiodini P, Georgoulias V, et al: Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non–small-cell lung cancer. J Clin Oncol 27:1836-1843, 2009

13. Azzoli CG, Temin S, Aliff T, et al: 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer. J Clin Oncol 29:3825-3831, 2011

14. Paz-Ares LG, de Marinis F, Dediu M, et al: PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non–small-cell lung cancer. J Clin Oncol 31:2895-2902, 2013

15. Ciuleanu T, Brodowicz T, Zielinski C, et al: Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: A randomised, double-blind, phase 3 study. Lancet 374:1432-1440, 2009

16. Cappuzzo F, Ciuleanu T, Stelmakh L, et al: Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 11:521-529, 2010

17. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-957, 2009

18. Gridelli C, Ciardiello F, Gallo C, et al: First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non–small-cell lung cancer: The TORCH randomized trial. J Clin Oncol 30:3002-3011, 2012

19. Maruyama R, Nishiwaki Y, Tamura T, et al: Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non–small-cell lung cancer. J Clin Oncol 26:4244-4252, 2008

20. Douillard JY, Shepherd FA, Hirsh V, et al: Molecular predictors of outcome with gefitinib and docetaxel in previously treated non–small-cell lung cancer: Data from the randomized phase III INTEREST trial. J Clin Oncol 28:744-752, 2010

21. Sun JM, Lee KH, Kim SW, et al: Gefitinib versus pemetrexed as second-line treatment in patients with nonsmall cell lung cancer previously

treated with platinum-based chemotherapy (KCSG-LU08-01): An open-label, phase 3 trial. Cancer 118: 6234-6242, 2012

22. Lee DH, Park K, Kim JH, et al: Randomized Phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. Clin Cancer Res 16:1307-1314, 2010

23. Garassino MC, Martelli O, Broggini M, et al: Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): A randomised controlled trial. Lancet Oncol 14:981-988, 2013

24. Ciuleanu T, Stelmakh L, Cicenas S, et al: Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): A randomised multicentre, open-label, phase 3 study. Lancet Oncol 13:300-308, 2012

25. Karampeazis A, Voutsina A, Souglakos J, et al: Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: A Hellenic Oncology Research Group (HORG) randomized phase 3 study. Cancer 119:2754-2764, 2013

26. Lazzari C, Novello S, Barni S, et al: Randomized proteomic stratified phase III study of second-line erlotinib (E) versus chemotherapy (CT) in patients with inoperable non-small cell lung cancer (PROSE). J Clin Oncol 31, 2013 (suppl 15s; abstr LBA8005

27. Lee CK, Brown C, Gralla RJ, et al: Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: A meta-analysis. J Natl Cancer Inst 105:595-605, 2013

28. Tassinari D, Scarpi E, Sartori S, et al: Noninferiority trials in second-line treatments of nonsmall cell lung cancer: A systematic review of literature with meta-analysis of phase III randomized clinical trials. Am J Clin Oncol 35:593-599, 2012

29. Qi WX, Shen Z, Lin F, et al: Comparison of the efficacy and safety of EFGR tyrosine kinase inhibitor monotherapy with standard second-line chemotherapy in previously treated advanced non-small-cell lung cancer: A systematic review and meta-analysis. Asian Pac J Cancer Prev 13:5177-5182, 2012

30. Jiang J, Huang L, Liang X, et al: Gefitinib versus docetaxel in previously treated advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials. Acta Oncol 50:582-588, 2011

31. Okano Y, Ando M, Asami K, et al: Randomized phase III trial of erlotinib (E) versus docetaxel (D) as second- or third-line therapy in patients with advanced non-small cell lung cancer (NSCLC) who have wild-type or mutant epidermal growth factor receptor (EGFR): Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 31, 2013 (suppl 15s: abstr 8006)

32. Zhu CQ, da Cunha Santos G, Ding K, et al: Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR. 21. J Clin Oncol 26:4268-4275, 2008

33. Coudert B, Ciuleanu T, Park K, et al: Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. Ann Oncol 23:388-394, 2012

34. Kim ES, Herbst RS, Wistuba II, et al: The BATTLE trial: Personalizing therapy for lung cancer. Cancer Discov 1:44-53, 2011

35. Gerber DE, Rasco DW, Le P, et al: Predictors and impact of second-line chemotherapy for advanced non-small cell lung cancer in the United States: Real-world considerations for maintenance therapy. J Thorac Oncol 6:365-371, 2011

36. Sacher AG, Le LW, Lau A, et al: Metastatic NSCLC: Treatment patterns, outcomes, and costs of newer agents. J Clin Oncol 30, 2012 (suppl 15s; abstr 7606)

37. Hensing TA, Schell MJ, Lee JH, et al: Factors associated with the likelihood of receiving second line therapy for advanced non-small cell lung cancer. Lung Cancer 47:253-259, 2005

DOI: 10.1200/JCO.2013.54.4270; published online ahead of print at www.jco.org on May 19, 2014

Acknowledgment

We thank Harold Burstein, MD, and Joan Schiller, MD, for their editorial contributions.